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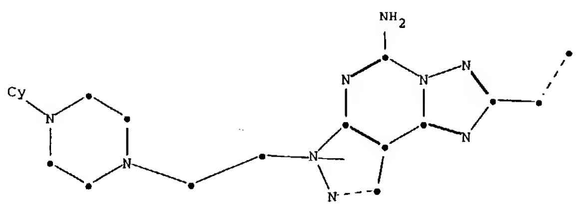

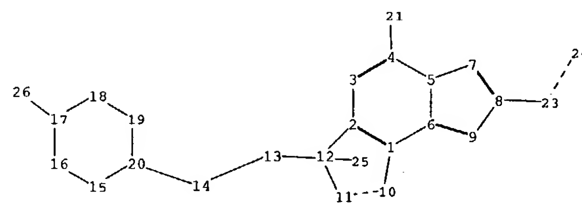

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Progress in pursuit of therapeutic A2A antagonists: the adenosine A2A receptor selective antagonist KW6002: research and development toward a novel nondopaminergic therapy for Parkinson's disease.

Kase H, Aoyama S, Ichimura M, Ikeda K, Ishii A, Kanda T, Koga K, Koike N, Kurokawa M, Kuwana Y, Mori A, Nakamura J, Nonaka H, Ochi M, Saki M, Shimada J, Shindou T, Shiozaki S, Suzuki F, Takeda M Yanagawa K, Richardson PJ, Jenner P, Bedard P, Borrelli E, Hauser R Chase TN; KW-6002 US-001 Study Group.

Kyowa Hakko Kogyo Co. Ltd., Tokyo, Japan. hiroshi.kase@kyowa.co.jp

Research and development of the adenosine A2A receptor selective antagoni KW6002 have focused on developing a novel nondopaminergic therapy for Parkinson's disease (PD). Salient pharmacologic features of KW6002 were investigated in several animal models of PD. In rodent and primate models, KW6002 provides symptomatic relief from parkinsonian motor deficits without provoking dyskinesia or exacerbating existing dyskinesias. The majc target neurons of the A2A receptor antagonist were identified as GABAergic striatopallidal medium spiny neurons. A possible mechanism of A2A receptc antagonist action in PD has been proposed based on the involvement of striat and pallidal presynaptic A2A receptors in the "dual" modulation of GABAergic synaptic transmission. Experiments with dopamine D2 receptor knockout mice showed that A2A receptors can function and anti-PD activitie of A2A antagonists can occur independent of the dopaminergic system. Clinical studies of KW6002 in patients with advanced PD with L-dopa-relate motor complications yielded promising results with regard to motor sympton relief without motor side effects. The development of KW6002 represents th first time that a concept gleaned from A2A biologic research has been applie successfully to "proof of concept" clinical studies. The selective A2A antagonist should provide a novel nondopaminergic approach to PD therapy.

Publication Types:

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- Review, Academic

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ELSEVIER SCIENCE FULL-TEXT ARTICLE

Inhibition of monoamine oxidase B by selective adenosine A2A receptor antagonists.

Petzer JP, Steyn S, Castagnoli KP, Chen JF, Schwarzschild MA, Van de Schyf CJ, Castagnoli N.

Department of Chemistry, Virginia Tech, Blacksburg, VA 24061-0212, USA

Adenosine receptor antagonists that are selective for the A(2A) receptor subtype (A(2A) antagonists) are under investigation as possible therapeutic agents for the symptomatic treatment of the motor deficits associated with Parkinson's disease (PD). Results of recent studies in the MPTP mouse mode of PD suggest that A(2A) antagonists may possess neuroprotective propertie: Since monoamine oxidase B (MAO-B) inhibitors also enhance motor functio and reduce MPTP neurotoxicity, we have examined the MAO-B inhibiting properties of several A(2A) antagonists and structurally related compounds i an effort to determine if inhibition of MAO-B may contribute to the observec neuroprotection. The results of these studies have established that all of the (E)-8-styrylxanthinyl derived A(2A) antagonists examined display significan MAO-B inhibitory properties in vitro with K(i) values in the low micro M to nM range. Included in this series is (E)-1,3-diethyl-8-(3,4-dimethoxystyryl)-' methylxanthine (KW-6002), a potent A(2A) antagonist and neuroprotective agent that is in clinical trials. The results of these studies suggest that MAO-l inhibition may contribute to the neuroprotective potential of A(2A) receptor antagonists such as KW-6002 and open the possibility of designing dual targeting drugs that may have enhanced therapeutic potential in the treatment of PD.

PMID: 12628657 [PubMed - indexed for MEDLINE]

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1: Drug News Perspect. 2003 Nov;16(9):597-604. Related Articles, Lir

The adenosine A(2A) receptor as an attractive target for Parkinson's disease treatment.

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Long-term L-dopa treatment of Parkinson's disease can lose its effectiveness and cause development of motor complications such as dyskinesia. Furthermore, L-dopa therapy does not address the fundamental pathological process of dopaminergic neurodegeneration in Parkinson's disease. This prompts a search for an alternative or complementary therapy for Parkinson's disease to overcome these limitations. During the last 5 years, the adenosine (2A) receptor has emerged as an attractive target for Parkinson's disease therapy, primarily because of its localized expression in striatum and motor enhancement function. Recent genetic and pharmacological studies indicate that A(2A) receptor antagonists also offer neuroprotective effects and may possibly modify chronic L-dopa-induced maladaptive responses in animal models of Parkinson's disease. This review summarizes multiple potential benefits of the A(2A) receptor blockade in treating the motor symptoms as well as the underlying dopaminergic neurodegeneration of Parkinson's diseas

Publication Types:

- Review
- Review, Tutorial

PMID: 14702141 [PubMed - indexed for MEDLINE]

1: Biosci Biotechnol Biochem. 2001 Jul;65(7):1447-57. Related Articles, Lir

J-STAGE

New aspects of physiological and pathophysiological functions o adenosine A2A receptor in basal ganglia.

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Pharmaceutical Research & Development Division, Kyowa Hakko Kogyo C Ltd., Tokyo, Japan. hiroshi.kase@kyowa.co.jp

There is now growing interest in the functional role of adenosine A2A receptors. Their distribution within the brain is restricted in the basal ganglia particularly abundant in the striatum, which are thought to play a crucial role in the control of motor behavior. Indeed, newly developed A2A receptor selective antagonists have a profound influence on motor functions, with anti Parkinsonian activities in several animal models. Striatal spiny neurons serve as a major anatomical locus for the relay of cortical information flow througl the basal ganglia. The GABA releasing projection neurons represent the A2A receptor-mediated main target of adenosine. The GABAergic synaptic neurotransmission is regulated by adenosine via A2A receptors on the presynaptic terminals. Blockade of this modulatory function by A2A antagonists could repair striatopallidal abnormal neuronal activities provokec by striatal dopamine depletion in the Parkinsonian state. A2A receptor antagonists provide a novel therapeutic potential for the treatment of Parkinson's disease.

Publication Types:

- Review
- Review, Tutorial

PMID: 11515525 [PubMed - indexed for MEDLINE]

Up

Adenosine and it's receptors

You might wish to make yourself a decent cup of coffee, before you puzzle over the intricacies of the adenosine receptor! Caffeine in coffee appears to improve your ability to handle mental tasks, mainly through its inhibition of the adenosine receptor. The side effects of excessive intake of caffeine (diuresis, tremor and agitation) are typical of interference with adenosine receptors.

The adenosine receptors

Adenosine is prevalent throughout the body. Adenosine may be important in the function of normal nerve cells, in controlling cell proliferation, and as a signal of inflammation. Levels rise rapidly in *ischaemic* tissue due to adenosine kinase inhibition, and mediate ischaemic pre-conditioning, where a prior, brief episode of organ ischaemia protects against subsequent ischaemia! *Inflamed tissues* also release adenine *nucleotides* which are converted to adenosine. Cells that release these nucleotides include platelets, mast cells, nerves and the endothelium. Ecto-nucleotidases (CD39, CD73) then turn the nucleotides into adenosine.

{Fond on the endothelial surface, on lymphocytes, and on Langerhans cells, CD39 is otherwise known as ATPDase, or ENTPD2. It converts ATP and ADP to AMP. CD39 may be both pro- and anticoagulant, due to its complex effects on platelets! Lack of CD39 causes an enhanced inflammatory response in some experimental models, but with impaired T-cell responses. A 5' nucleotidase found on lymphocytes and endothelium, CD73 dephosphorylates nucleoside monophosphates to nucleosides. It thus makes adenosine, but may have many other functions }.

The four adenosine receptors which detect local changes in adenosine concentration are called A1, A2A & B, and A3. They are "seven-spanning" proteins coupled to various G-proteins. As one might expect, things are hellishly complex, as interactions occur with a vast array of other receptors. A2 receptors work on G_s, but A1 and A3 interact with G_i and G_o. There may be other G-protein interactions. Here are the four receptors in more detail:

1. Stimulation of **A1** receptors inhibits nerve cells, and these receptors also mediate the profound effects of adenosine on the heart. A1 receptors are responsible for the important process of `pre-conditioning'.

   By lowering heart rate, and, especially, slowing AV nodal conduction, adenosine causes `pharmacological cardioversion', of particular use in AV nodal re-entrant tachycardia, but with other anti-arrhythmic uses too. In the basal forebrain accumulation of adenosine (seen with prolonged wakefulness) is thought to inhibit cholinergic cells and induce sleep! A1 receptors also promote vasoconstriction. A1 receptors in the preglomerular vessels and tubules regulate renal fluid balance. Antagonists to A1 receptors cause diuresis and natriuresis without major changes in GFR. A1 antagonists decrease afferent arteriolar pressure.

2. **A2A** stimulation is anti-inflammatory --- the receptors are used to *sense excessive tissue inflammation*! These receptors also enhance neural communication, promote coronary vasodilatation, and have *anti-platelet effects*. CNS effects may be favourable in patients with Huntington's chorea, and agonists may also inhibit psychosis. A2A agonists cause profound vasodilatation, with a corresponding increase in plasma renin activity.

3. **A2B**: similar to A2A, but not identical, these are perhaps the most poorly characterised of the adenosine receptors. Signalling pathways may differ substantially. A2B is found on the human mast cell --- this may be particularly relevant to the management of asthma --- but A2B receptors are widespread throughout the body. Like A2A receptors, A2B promote vasodilatation.

4. **A3**: This is the Janus of the adenosine receptors. A variety of effects have been claimed, but other reports then allege completely opposite effects! Many of these conflicting reports seem to be explained by use of different concentrations of agonists, or cells at different stages of their lifespan. A3 is a key receptor in both stimulation and inhibition of cell growth (stimulates many normal cells in micromolar concentrations, induces apoptosis at higher concentrations in both normal and tumour cells). Low concentrations may have antiproliferative effects on tumour cells despite stimulating bone marrow cells! Others claim that adenosine may have many *bad* effects, promoting tumour growth and angiogenesis. A3 receptor stimulation (at various concentrations, and over various time-spans) may be harmful *or* beneficial in cerebral ischaemia! There is some evidence that, like the A1 receptor, the A3 receptor may contribute to pre-conditioning.

Potential therapeutic use

Both adenosine agonists and antagonists have many potential uses. Relatively few of these potential uses have been realised.

The heart

The role of adenosine in treating supraventricular tachyarrhythmias is now well-accepted. Due to the inhibitory effect of adenosine on the AV node (and consequent cardiac standstill), adenosine is the drug of choice for AV nodal re-entrant tachycardia. Adenosine is rapidly degraded, so the duration of cardiac standstill is usually just a few seconds, but larger doses cause more prolonged arrest.

- Adenosine is probably important in myocardial pre-conditioning. Following a brief ischaemic insult, there is bimodal preconditioning --- the latter, prolonged phase is largely mediated by adenosine. A1 (and probably A3) agonists replicate this protection. Mechanisms are unclear but may involve mitochondrial Mn-SOD, 27kDa HSP, and opening of K_{ATP} channels. Mitochondrial K_{ATP} channels may be more important than sarcolemmal ones.

- Proarrhythmia may occur --- AF and life-threatening ventricular arrhythmias. Atrial fibrillation/flutter has also been seen in children, worryingly also in WPW.

  Adenosine may even be useful in heart failure. Adenosine induces collateral circulation, reduces noradrenaline/endothelin release and renin/angiotensin/aldosterone axis activation, and protects against reperfusion.

Neurology

In neurology adenosine receptors may be important in Parkinson's disease, pain states, drug addiction,

schizophrenia, and even Alzheimer's disease. There is fairly convincing prospective epidemiological evidence of a protective effect of caffeine against Parkinson's disease! Specific A2A **ant**agonists *may* be useful in Parkinson's disease. Caffeine and also more specific A2A antagonists attenuate PD in mouse models, and they also cause symptomatic improvement in PD.

{ Expression of A2A receptors in the brain is predominantly in the basal ganglia, especially the striatum. At a receptor level, there appears to be antagonism between A2A and D2 dopaminergic receptors, and also between A1 and D1 receptors. This is important, because dopamine's effect seems to be in allowing initiation of movement. Adenosine receptor stimulation antagonises this effect.

Two sets of pathways are notable:

1. GABAergic striatopallidal neurones which rely on A2A/D2, and
2. striatonigral and striatoentopeduncular neurones, which use A1/D1!

The neurological literature is a little confusing, as a lot of emphasis has been placed on specific antagonists of A2A, despite observations that the entopeduncular nucleus and substantia nigra also seems rather important in initiation of movement! This D2 bias is reflected in the clinical emphasis on D2 dopaminergic agonists in the management of Parkinson's disease. A lot of the emphasis on selective D2 agonism seems to be because current theories about the pathogenesis of treatment-related dyskinesias emphasise intermittent D1 receptor stimulation. Others disagree rather vehemently. L-DOPA induced dyskinesias may in fact be related to abnormalities of basal ganglia opioid transmission. }

There seems to be a lot of controversy about the role of adenosine in stroke.

Pain

Adenosine receptor agonists might just become important in pain management. Intrathecal adenosine is a potential treatment for neuropathic pain --- adenosine 0.5 or 2.0mg by this route antagonises capsaicin-induced hyperalgesia and allodynia.

Asthma

Most inflammatory cells involved in asthma and COPD exacerbation express adenosine receptors. One of the mechanisms of action of aminophylline in asthma may be through inhibition of adenosine A2B receptors (Ki 13μM, The A2B agonist enprofylline has similar effects). A1, A2B and A3 receptor stimulation appear to induce bronchospasm in asthmatics and animal models of asthma, while A2A receptors have no/opposite effects. A1 effects are mast-cell independent, while A2B and A3 effects require mast cells. It's been said that A1 receptor down-regulation, A2A receptor activation and A2B blockade may be useful in asthma. In asthma, responsiveness to inhaled adenosine is a good marker of airway inflammation. Adenosine may even be a more specific bronchoprovocant than methacholine or histamine.

Immune implications

- Adenosine accumulation and stimulation of (?A2) receptors has been implicated in the immunosuppression seen in critical illness

- A3 receptor stimulation may inhibit tumour growth, perhaps melanomas, colon or prostate carcinoma, and lymphomas. Peripheral blood monocytes produce G-CSF when stimulated by adenosine.

The kidney

A1 antagonists act as potassium-sparing diuretics and may protect against contrast-induced injury. A1 receptors are an absolute requirement for normal tubuloglomerular feedback (where increases in NaCl delivery at the macula densa heighten afferent arteriolar tone). It seems that A1 antagonists protect against decline in renal function seen with diuretic therapy, while augmenting the diuresis! Increased adenosine sensitivity (with increased vasoconstriction) may be important in the pathogenesis of contrast-induced nephrotoxicity.

Platelet effects

Effects have been well reviewed by Gessi et al. Platelets are rich in A2A receptors, and adenosine appears to have an anti-aggregatory effect when it stimulates these receptors. Study of these receptors on platelets is made difficult due to the presence of adenotin, a non-receptor protein that also binds A2 agonists, but A2A appears to be high-affinity. A2A knockout mice show increased platelet aggregation. Anti-coagulant effects of exogenously administered adenosine will necessarily be very brief.

Ectonucleotidases on endothelial cells may limit propagation of clot, preventing its extension over normal endothelium. They could do this by converting pro-aggregant ADP to adenosine, which inhibits platelet function by acting at A2A receptors.

Other effects

Adenosine may be important in sensory transmission in the gut: [News Physiol Sci. 2001 Oct;16:201-7. Unlocking mysteries of gut sensory transmission: is adenosine the key? Christofi FL]

Pharmacology

Receptor pharmacology is complex. A1 and A2A receptors are high affinity (reaction constants in nanomolar range). Interestingly enough, inverse agonism occurs at A1 receptors! A2B receptors are low-affinity. A lot of the pharmacological investigation of drugs that work at adenosine receptors has been on adenosine receptor antagonists. We will consider these first.

Receptor antagonists

Nonselective are e.g. methylxanthines; Lead compounds are adenosine and methylxanthine. Flavonoids (from a variety of dietary plants, and e.g. soy) inhibit adenosine receptor stimulation, when present in the micromolar range. Examples are galangin (A1, A2A, A3), pentamethylmorin (A3, Ki 2.65 μM), genistein (A1), hispidol (and other aurones; A1, Ki 350nM). Synthetic derivatives such as MRS 1067 are very A3 selective. Partial agonists/ antagonists may be present in *Hypericum perforatum* and *Valeriana officinalis*. Experimentally useful are: MRS1754 (A(2B) blocker), MRS1220 (A(3) blocker), MRE 3008F20 (human A(3) blocker), MRS1523 (rat A(3) blocker).

Agonists

The clinical potential of adenosine agonists seems to be limited, apart from the use of adenosine itself, mainly for its anti-arrhythmic potential in conditions such as AV nodal re-entrant tachycardia. Adenosine kinase inhibitors may act as indirect AR agonists.

Details

There is a vast array of drugs that act at the various receptors. Modifications of the pyrazolo-triazolo-pyrimidine nucleus give good receptor subtype specificity. Here's a brief summary of various adenosine receptors and their selective agonists and antagonists, modified after Feoktistov and Biaggioni.

Receptor	*Order of potency* §	*Agonists**	*Antagonists**
A1	R-PIA (0.001) > NECA (0.006) > IB-MECA (0.054) > CGS 21680 (2.6)	R-PIA, CPA TCPA, CVT-3146, CVT-510, GR 79236	DPCPX, N-0861, CVT-124 (=BG9719), KW-3902, FR166124, FK453, WRC-0571^{++}, CPX^{++}, FSCPX^{+}
A2A	NECA (0.01) = CGS 21680 (0.015) > IB-MECA (0.056) > R-PIA (0.124)	CGS 21680, APEC, 2HE-NECA	SCH 58261, ZM 241385, CSC, KF17837
A2B	NECA (2) > R-PIA (160) = IB-MECA (201) > CGS 21680 (1600)	None	Enprofylline, IPDX, MRS 1754
A3	IB-MECA (0.001) > NECA (0.113) = R-PIA (0.158) > CGS 21680 (0.584)	IB-MECA, CI-IB-MECA, 3'-Aminoadenosine-5'-uronamides	MRS 1067, MRS 1097 L-249313, L-268605, CGS15943, KF26777, other**

* selective; $^{+}$ irreversible! $^{++}$ inverse agonist activity too! ** [J Med Chem. 2002 Aug 15;45(17):3579-82].
§ Potencies are K_i's (μM)

Non-receptor effects of adenosine

Some of the effects of adenosine appear to be mediated by "Non-receptor adenosine signalling"! Using this mechanism, adenosine can induce apoptosis during neuronal growth, and also can *prevent* apoptosis in more mature sympathetic neurones!

References

Numerous references are embedded in the HTML text above. In addition:

1. We have elsewhere looked at ATP and adenosine actions, pharmacokinetics and use!
2. An extensive website at the University of Leiden: http://www.medchem.leidenuniv.nl/

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5. Gessi S, Varani K, Merighi S, Ongini E, Borea PA. *A(2A) adenosine receptors in human peripheral blood cells* Br J Pharmacol. 2000 Jan;129(1):2-11.
6. Feoktistov I, Biaggioni I: Pharmacol Rev. 1997 Dec;49(4):381-402 *Adenosine A2B receptors.*

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